

WHAT IS CLAIMED IS:

1 1. A method of making a non-replicating anti-bacterial phage, said
2 method comprising the step of producing said anti-bacterial phage in a host production
3 bacterium, wherein said anti-bacterial phage is unable to replicate in a target bacterium and
4 wherein said anti-bacterial phage inhibits growth of said target bacterium.

1 2. The method of Claim 1, wherein said non-replicating anti-bacterial
2 phage is unable to replicate in said target bacterium because:

3 the nucleic acid of said anti-bacterial phage is inactivated or removed;
4 said phage comprises a mutation and cannot assemble into a replication
5 competent phage in said target bacterium, but said host production bacterium is a
6 complementing host bacterium that is able to complement, including with a helper phage,
7 said mutation of said anti-bacterial phage and allow replication of said anti-bacterial phage in
8 said complementing host production bacterium;

9 said phage comprises DNA containing a restriction site sensitive to a
10 restriction enzyme activity, said activity found in said target bacterium but absent in said host
11 production bacterium; or

12 said phage expresses in said target bacterium a function early in
13 infection which prevents DNA or phage replication, but fails to express said function in said
14 host production bacterium.

1 3. The method of Claim 2, wherein:

2 said mutation is temperature sensitive at a non-permissive temperature,
3 and said complementing host production bacterium complements said mutation at said non-
4 permissive temperature;

5 a nucleic acid of said non-replicating anti-bacterial phage comprises a
6 mutation and cannot assemble into a replication competent phage, further comprising a step
7 of supplying a complementing helper phage that can complement said mutation of said anti-
8 bacterial phage and allow replication of said anti-bacterial phage in said host production
9 bacterium;

10 said mutation is a substantial deletion, and said complementing host
11 production bacterium complements said deletion mutation, e.g., with a gene in said host
12 production bacterium or a helper phage;

1 5. A pharmaceutical composition comprising an anti-bacterial phage,
2 wherein said anti-bacterial phage inhibits growth of a target bacterium, and wherein said anti-
3 bacterial phage has diminished replication activity in said target bacterium.

- 1 6. The composition of Claim 5, wherein:
 - 2 said anti-bacterial phage exhibits no DNA or phage replication activity
 - 3 in said target bacterium;
 - 4 said anti-bacterial phage comprises less than 98% of the complexity of
 - 5 the nucleic acid of an intact phage;
 - 6 said anti-bacterial phage comprises less than 20% of the nucleic acid
 - 7 content of an intact parental phage;
 - 8 said anti-bacterial phage comprises less than 2% of the nucleic acid
 - 9 content of the intact parental phage;
 - 0 said anti-bacterial phage does not contain detectable nucleic acid;
 - 1 said anti-bacterial phage comprises an intact phage comprising nucleic
 - 2 acid with a reduced replication capacity in said target bacterium;
 - 3 said anti-bacterial phage comprises a tail portion of a tailed phage,
 - 4 including a myoviridae or siphoviridae phage;
 - 5 said anti-bacterial phage comprises an electron microscope
 - 6 morphologically identifiable tail portion of a tailed phage;
 - 7 said anti-bacterial phage consists essentially of a tail portion of a
 - 8 myoviridae or siphoviridae phage;
 - 9 said composition further comprises a therapeutically compatible buffer
 - 0 or excipient;

the said composition further comprises a second therapeutic agent, including an anti-microbial, antibiotic, or inflammatory agent;

said anti-bacterial phage is made by a method comprising the steps of:

- a) amplifying a phage in a host production bacterium,
- b) harvesting said phage from said host production bacterial

c) depleting or inactivating substantially all of the nucleic acids from said phage, thereby producing said anti-bacterial phage:

said anti-bacterial phage is made by a method comprising steps of:

- a) amplifying a phage in a host production bacterium, and
- b) harvesting said phage from said host production bacterial

culture before substantial amounts of intact phage are produced or assembled, thereby producing said anti-bacterial phage; or

said anti-bacterial phage is made by a method comprising steps of:

- a) amplifying a phage in a host production bacterium, and
- b) harvesting said phage from said host production bacterial

culture, wherein a nucleic acid of said anti-bacterial phage comprises a mutation and cannot assemble into a replication competent phage, and wherein said host production bacterium is a complementing host production bacterium that is able to complement said mutation of said anti-bacterial phage and allow replication of said anti-bacterial phage in said complementing host production bacterium, including where said complementing results from a helper phage, thereby producing said anti-bacterial phage.

7. A method of treating a bacterial population:

in a subject in need of said treatment, said method comprising:

3 administering a therapeutically effective amount of a composition of Claim 5;

in a subject, said method comprising administering to said subject a composition of claim 5, or

5 effective amount of a composition of Claim 5.

8. The method of Claim 7, wherein:

said bacterial infection is caused by said *Leptospiral* bacteria.

the said subject is a human

said subject is a primate, a female, and a human.

1 10. The pharmaceutical composition of Claim 9, wherein:
2 said target bacterium is identified or diagnosed, including an
3 Escherichia, Staphylococcus, Pseudomonas, or Streptococcus bacterium;
4 said genetically incompetent anti-bacterial phage lacks a full
5 complement of genetic material;
6 said genetically incompetent anti-bacterial phage has a mutation and
7 cannot assemble into replication competent phage in said target bacterium;
8 said genetically incompetent anti-bacterial phage comprises nucleic
9 acid with a reduced replication capacity, e.g., comprising a mutation, including a missense,
10 termination, frameshift, conditional, deletion, or insertion mutation, in a critical phage
11 replication function;
12 said genetically incompetent anti-bacterial phage consists essentially of
13 a tail portion from a tailed phage, including a myoviridae or siphoviridae phage; or
14 said pharmaceutical composition further comprises an excipient,
15 buffer, or a second therapeutic or anti-microbial agent.

1 11. A method of using a pharmaceutical composition of Claim 9 to treat a
2 bacterial infection in a subject in need of such treatment, said method comprising a step of
3 administering a therapeutically effective amount of said pharmaceutical composition.

said subject is a primate, a food, work, display, or companion animal;
 said pharmaceutical composition is administered systemically,
parenterally, orally, topically, or by inhalation, catheter, or drain tube; or
 said pharmaceutical composition is administered in combination with a
second therapeutic or anti-bacterial agent, e.g., an anti-microbial, inflammatory, or anti-
inflammatory agent.

13. A method of identifying an anti-bacterial phage that is unable to replicate in a selected target bacterium, said method comprising the steps of:

- culturing said target bacterium; and
- testing various potential anti-bacterial phage, including genetic variants of a phage, for combined properties of inhibition of growth on said target bacterium, and absence of capacity to replicate phage DNA or phage in said target bacterium.

14. An anti-bacterial phage that is identified using said method of Claim 13, wherein said phage inhibits growth of a target bacterium and is unable to replicate in said target bacterium. [product by process claim, but might be difficult to enforce]

15. A method of producing non-replicating anti-bacterial phage comprising the steps of:

replicating phage in a host production bacterium,

harvesting said phage from said host production bacterial culture, and

removing substantially all of the function of the nucleic acids from said phage, thereby producing said non-replicating anti-bacterial phage.

16. The method of Claim 15, wherein:

 said anti-bacterial phage is a tailed phage, including a myoviridae or siphoviridae phage;

 said nucleic acids are removed by steps of:

 a) separating tails from heads of tailed phage fragments, and

 b) isolating said tails;

 said function of said nucleic acids is removed by steps of:

 a) harvesting said phage before tails and heads have assembled to form an intact phage, and

 b) isolating said tails;

1 19. The complementing host or helper phage of Claim 18B, wherein said
2 host production bacterium or helper phage encodes one or more genes which complement
3 said mutation in said anti-bacterial phage, thereby allowing said anti-bacterial phage to
4 replicate in said producing bacterium.

1 20. A defined dose therapeutic anti-bacterial composition comprising a
2 phage protein derived from an intact parental phage or prophage, said anti-bacterial
3 composition capable of killing a target bacterium, said anti-bacterial composition exhibiting
4 less than 20% DNA or phage replication activity in said target bacterium, when compared to
5 said intact parental phage or prophage.

1 21. The composition of Claim 20, wherein:
2 said composition exhibits less than 5% replication activity in said
3 target bacterium when compared to said intact parental phage;
4 said anti-bacterial phage exhibits diminished capacity to transmit toxin
5 genes in said target bacteria when compared to intact phage in said host bacterium;
6 said anti-bacterial composition exhibits diminished immunogenicity
7 compared to said intact phage from a host bacteria upon administration to a mammal;
8 said anti-bacterial phage exhibits no substantial or detectable DNA or
9 phage replication activity in said target bacterium;

1 22. A method of treating a bacterial colonization in a eukaryote
2 experiencing colonization by said target bacterium, said method comprising administering a
3 composition of Claim 20 to said eukaryote.

23. The method of Claim 22, wherein:

 said eukaryote is a mammal, including a primate;

 said eukaryote is a food, work, display, or companion animal;

 said target bacterium is a pathogenic, nosocomial, or pyogenic

 said target bacterium is an Escherichia, Staphylococcus, Pseudomonas, us bacterium;

 said composition is administered systemically, parenterally, orally, y inhalation, catheter, or drain tube;

 said colonization has already been treated with an anti-microbial or

 said colonization has been diagnosed to be susceptible to the selected

 said eukaryote is also inoculated with another bacterium to replace said

24. A therapeutic anti-bacterial composition comprising a genetically hage wherein said phage kills a target bacterium.

1 25. The composition of Claim 24, wherein:
2 said phage lacks detectable nucleic acid;
3 said phage comprises a chemically or physically damaged nucleic acid;
4 said phage lacks a functional gene necessary to replicate phage DNA
5 in said target bacterium, or contains a gene which prevents replication of phage DNA in said
6 target bacterium (restriction/modification or phage exclusion system);
7 said phage comprises a missense, termination, frameshift, conditional,
8 deletion, or insertion mutation in a gene necessary for phage replication, e.g., capacity to
9 infect, assemble, produce, or release intact phage, or contains a gene whose expression
10 prevents phage replication (restriction/modification system);
11 said phage comprises a tail protein from a tailed phage;
12 said composition is used therapeutically to treat a food, work, display,
13 or companion animal, or primate;
14 said target bacterium is a pathogenic bacterium, e.g., an Escherichia,
15 Staphylococcus, Pseudomonas, or Streptococcus bacterium;

16 said composition is administered systemically, parenterally, orally,
17 topically, or by inhalation, catheter, or drain tube; or
18 said composition is administered in combination with a second
19 therapeutic agent, including an anti-bacterial, inflammatory, or anti-inflammatory agent.